ORIGINAL ARTICLE

Insight Atherosclerosis

HASAN RAZA*, SHAH MURAD**, ANIS FATIMA***, *SAMINA KARIM***

ABSTRACT

Atherosclerosis eventually causing myocardial infarction or heart attack is leading cause of mortality in developed and developing countries in the world. Well recognized and explained risks for development of atherosclerosis include already having family history of the disease, old age, male gender, sedentary life style, chronic continuous smoking and/or intake of alcohol, blood lipid levels, body weight and blood pressure. So the research study was planned to examine the effects of niacin on blood pressure, body weight, bad cholesterol; i.e. LDL-cholesterol and good cholesterol; i.e. HDL-cholesterol. It was single blind placebo-controlled research study, which was conducted at Jinnah Hospital, Karachi, from June 2009 to December 2009. Forty male and female hyperlipidemic patients were included in the research study, among which 20 patients were on placebo as control group, and 20 were on tablet Niacin, 2.25 grams daily, in divided doses for the period of three months. Patients with diabetes mellitus, peptic ulcer, renal disease, hepatic disease, hypothyroidism and alcoholism were excluded from the study. Body weight and blood pressure of patients were recorded at fortnightly visit. LDL-Cholesterol was calculated by Friedwald formula (LDL= TC- (TG/5 + HDL-C). Serum HDL-cholesterol was determined by direct method. Serum cholesterol and triglycerides were estimated by the enzymatic calorimetric method. Data regarding results were expressed as the mean ± SD and "t" test was applied to determine statistical significance of results. A probability value of <0.05 was the limit of significance. Three patients were dropped from the study due to side effects of Niacin. In three months of treatment with 2.25 grams of niacin HDL-cholesterol increased from 36.41±1.96 to 43.70±1.81 mg/dl, which was highly significant change when analyzed statistically. Niacin has decreased LDL-Cholesterol from 182.58±8.74 mg/dl to 119.29±4.08 mg/dl, which was highly significant (P<0.001), when compared statistically by paired "t" test. Overall percentage (%) changes from day-0 to day-90 were 34.66. Interest also attaches to our findings that Niacin has also reduced Blood Pressure. Difference between mean values of systolic and diastolic blood pressure at day-0 and day-90 were found highly significant (P<0.001). Body weight was reduced from 66.29±194 kg to 64.79±1.82 kg in three months. This change was significant (P<0.01). We concluded from the research study that niacin decreases blood pressure, body weight and LDL-Cholesterol and increases HDL-cholesterol in primary hyperlipidemic patients.

Key words: Blood Pressure. Body Weight. HDL-C. LDL-C. Niacin.

INTRODUCTION

Atherosclerotic disease of both coronary and peripheral arteries appears to be a dynamic process. Elevated serum lipids and lipid carrying lipoproteins cause atherosclerosis, eventually leading to myocardial infarction[1]. Elevation of LDL-Cholesterol is particularly associated with risk of coronary artery disease. Moderately high levels of serum triglycerides with low levels of blood HDL-cholesterol is another scientifically well proved risk for developing atherosclerosis[2]. It is well explained that atherosclerosis, if not stopped at earlier steps may lead to development of myocardial infarction or heart attack[3,4]. Despite substantial medical progress in the past three decades, coronary heart diseases remain the major health problem in most of the industrialized countries. The disease remains a common cause of morbidity and mortality throughout the world. Each 1% increase in the serum cholesterol concentration results in 2-3% increase in CHD risk. The levels below 200 mg/dl are classified as desirable blood cholesterol, those 200 to 239 mg/dl as borderline high blood cholesterol and those 240 mg/dl and above as high blood cholesterol. The cut point that defines high blood cholesterol (240 mg/dl) is a value above which risk of CHD rises steeply. The cut points recommended are uniform for adult men and women of all ages[1-2,5-7]. There are various drugs which decrease total cholesterol, triglycerides, LDL-Cholesterol and increase HDL-Cholesterol in primary hyperlipidemic patients, but nicotinic acid is the best LDL-Cholesterol lowering agent among the lipid lowering drugs. Nicotinic acid has another beneficial effect that it reduces body weight and blood pressure.

Department of Biochemistry*, Pharmacology**, Aanatomy***Lahore Medical & Dental College
Correspondence to Dr. Hasan Raza, Assistant Professor of Biochemistry

Niacin increases HDL-Cholesterol by reducing its catabolism. It also decreases plasma fibrinogen levels and increase tissue plasminogen activator. All of these factors influence the process of atherogenesis and coronary heart disease.[8] Niacin inhibits the activity of lipoprotein lipase causing decrease in lipolysis and so decreased VLDL secretion from hepatocytes. Factors responsible for decreased production of VLDL include inhibition of lipolysis with a decrease in free fatty acids in plasma, decreased hepatic esterification of triglycerides, and a possible direct effect on the hepatic production of apolipoprotein-B[9]. Niacin is responsible for production of prostaglandin D-2 in vascular endothelium, which causes vasodilatation, the mechanism of action of the drug proved to lower systolic and diastolic blood pressure[10].

SUBJECTS AND METHOD

The research was conducted at Jinnah Hospital, Karachi, from June to December 2009. 40 patients of primary hyperlipidemia were enrolled for the research, selected from ward and OPD of Jinnah Hospital, Karachi. Male and female primary hyperlipidemic patients of 17 to 70 years age were selected. Patients with diabetes mellitus, peptic ulcer, renal disease, hepatic disease, hypothyroidism and alcoholism were excluded from the study by available laboratory investigation, history and clinical examination. After explaining the limitations, written consent was obtained from all participants. This research study was started after approval by Research Ethics Committee, Jinnah Hospital, Karachi. The study period consisted of 90 days with fortnightly follow up visits. The required information like name, age, sex, occupation, address, previous medication, date of follow up visit and laboratory investigations, etc of each patient was recorded on a proforma, especially designed for this study. Initially a detailed medical history and physical examination of all patients were carried out. All the base line assessments were taken on the day of inclusion (Day-0) in the study and a similar assessment was taken on Day-90 of research design. After fulfilling the inclusion criteria patients were randomly divided into two groups, i.e.Drug-1(tab: Niacin 2.25gm) and Drug-2 (placebo capsules, containing equal amounts of partly grinded wheat) groups. Patients of drug-1 group were advised to take Tab: Niacin (250 mg), half tablet thrice daily, after meal for 2 days, then by increasing the dose one tablet, TID, after meal for 2 days, then 2 tablets, thrice daily after meal for 2 days, then the maintenance dose of 3 tablets, thrice daily, till end of the study period, i.e. up to day-90. This regimen of dose of drug (called titration of Niacin) was applied due to avoidance of it's adverse effects produced by starting with higher doses of the Niacin.17 Patients of drug-2 group were provided placebo capsules, i.e. three capsules, TID, after meal for 90 days. Patients were called every 2 weeks for follow up to check blood pressure, weight, pulse rate and general appearance of the individual. Drug compliance to the regimen was monitored by interview and counseling at each clinical visits. Serum LDL-cholesterol was calculated by Friedwald formula (LDL-Cholesterol = Total Cholesterol-(Triglycerides/5 +HDL-Cholesterol). Data were expressed as the mean ± SD and "t" test was applied to determine statistical significance as the difference. For non significant results P-value >0.05 was used and for significant to highly significant results P-value <0.01 and <0.001 was used in the research.

RESULTS

When results were being compiled, it was observed that three patients withdrew from group-1 (Niacin group) due to side effects of the drug like flushing, sensation of heat, and headache. So, out of forty, 37 patients completed the study period, that was three months. Tables showing base line and post treatment values are self explanatory. When results were summed up and test parameters were compared, it was seen that, after three months of treatment with niacin, LDL-cholesterol decreased from 182.58±8.74 mg/dl to 119.29±4.08 mg/dl, which is highly significant (P<0.001). The overall percentage change from day-0 to day-90 was -34.66, as shown in table no: 1. In placebo group at day-0, LDL-cholesterol level was 150.75±2.67 mg/dl, which decreased to 148.80±2.28 mg/dl, which is non-significant (P>0.05).The overall percentage decrease in the parameter was -1.29, as shown in table no 2. The difference between mean values among placebo group and Niacin group is 33.4, which is highly significant (<0.001) as shown in the table 3. Niacin has increased HDL-cholesterol from 36.41±1.96 to 43.70±1.81 mg/dl, which is highly significant change (P-value <0.001). In percentage it is 20.02% increase. Systolic blood pressure reduced from 125.88±3.48 mm of Hg to 119.70±3.13 mm of Hg in three months. Diastolic blood pressure reduced from 89.11±1.92 to 84.70±1.74 mm of Hg in this duration of treatment with 2.25 grams of Niacin. These changes in both, systolic and diastolic blood pressure are highly significant (P<0.001). Body weight reduced from 66.29±1.94 kg to 64.79±1.82 kg, which is also highly significant (P<0.001) when compared with placebo group.

ORIGINAL ARTICLE

Table : Difference of effects of drug on body weight, systolic, diastolic blood pressure, LDL and HDL-Cholesterol between placebo and niacin group of patients in 3 months of treatment.

	Placebo Group (20 patients)			Drug Group (17 patients)			
Parameter	**Pre-treatment**	**Post-treatment**	**P Value**	**Pre-treatment**	**Post-treatment**	**P Value**	**Difference in groups**
Body weight	69.35±1.76	69.17±1.68	>0.05	66.29±1.94	64.79±1.82	<0.001	2.01%
Systolic BP	122.75±219	120.75±2.18	>0.01	125.88±3.48	119.70±3.13	<0.001	3.28%
Diastolic BP	84.25±1.99	82.00±1.82	>0.01	89.11±1.92	84.70±1.74	<0.001	2.27%
LDL-C(mg/dl)	150.75±2.67	148.80±2.28	>0.05	182.58±8.74	150.41±6.94	<0.001	33.4%
HDL-C mg/dl)	35.50±1.13	35.75±1.07	>0.05	36.41±1.96	43.70±1.81	<0.001	19.32%

Key:*(Drug Group is on niacin 2.25 gm, ± indicates standard error of mean, BP stands for blood pressure, Body weight is measured in kilograms, blood pressure is measured in mm of Hg, P Value >0.05 indicates non significant, P Value <0.01 indicates significant, P Value <0.001 indicates highly significant, Figures in parentheses indicate number of patients)*

DISCUSSION

Drop out ratio in our study was 9% and most of the patients discontinued treatment due to development of side effects like flushing, urticaria and sensation of heat in the body. Other patients were convinced for continuing therapy, by taking aspirin 250 mg, before taking 1st dose of niacin at morning, every day. There are various drug groups which are used as hypolipidemic agent and among all lipid lowering drugs, niacin appears to be the best HDL upraising and LDL lowering agent. In our research, HDL-cholesterol increased from 36.41±1.96 to 43.70±1.81 mg/dl and LDL-Cholesterol levels decreased by 34.66% in men and women with high LDL-C levels treated with 2.25 grams of Niacin. Reduction in body weight was 2.26%. Systolic blood pressure decreased 4.90% and diastolic blood pressure reduced 4.94% in three months of treatment with same dose of niacin as used in LDL lowering and HDL upraising dose. These results match with the results of study conducted by S. Lamon-Fava et al[11] who observed almost same changes in LDL-Cholesterol, body weight and blood pressure. HDL-cholesterol is not increased as much as in our research study. Their research proved only 11.09% increase in HDL cholesterol. In their study LDL-C reduced 29.75%, systolic BP 2.89%, diastolic BP 3.98% and body weight 2.94%, in 90 days of treatment with three grams of niacin in 47 primary hyperlipidemic patients. Results of study conducted by L. H. Zhang et al[12] also match with our study results. In their results LDL cholesterol reduced 31.98%, systolic blood pressure 3.87%, diastolic blood pressure 3.87% and body weight 2.91%. They observed remarkable increase in HDL cholesterol in 15 female hyperlipidemic patients when two grams of niacin was used for 4 months. J. G. Richman et al[13] observed that niacin is very effective among all lipid lowering drugs, that can reduced LDL cholesterol and increase HDL cholesterol remarkably. They proved 30.12% reduction in low density lipoprotein cholesterol and 20.56% increase in high density lipoprotein cholesterol when 3 grams of niacin was used in 20 hyperlipidemic patients for three months. These results also coincide with our results regarding LDL and HDL cholesterol. Results of research study conducted by J. Mckenny[14] are in contrast with our results who observed only 12.99% decrease in LDL-Cholesterol by using three grams of niacin in 13 hyperlipidemic patients for the period of three months. In his observation systolic and diastolic blood pressure was reduced 1.19 and 1.78% respectively. Body weight was reduced 2.90%. These findings do not match with our results, except body weight. The reason for difference may be due to small sample size and environmental factors. His patients strictly followed step-I diet, along with taking drug. M. E. Mcgovern[15] proved 27.03% reduction in concentration of LDL cholesterol and 10.71% increase in HDL cholesterol. This observation is in contrast with our observation, probably due to small sample size and low dose of the drug in our study. He used 4.4 grams of niacin in 87 hyperlipidemic patients for the period of 8 months. L. Saucan and E. A. Brinton[16] used 2 grams of niacin in 20 hyperlipidemic patients for 3 months and observed 20% increase in HDL cholesterol and only 13% decrease in LDL cholesterol. Result of one of the parameter that is HDL cholesterol matches with our result but in another parameter that is LDL cholesterol results of their study and our research results are in contrast. The reason of this contrast may be the cases of secondary hyperlipidemia, they included in their study. We excluded secondary hyperlipidemic patients in our research work. In their study 10 patients discontinued to take part in research as agreed initially. The reason for this remarkable dropout was urticaria, warmth feeling and redness on dependant parts of the body by taking

niacin. Mechanism by which aspirin blocks niacin-induced flushing and feeling of hotness is explained by T. Sakai et al[17]. Cyclo-oxyginase pathway is responsible for production of prostaglandin D2, which causes vasodilatation and feeling of warmth, when a person uses niacin. To avoid these effects, titration of dose of niacin must be followed or 100 mg aspirin may be used half an hour before taking each dose of niacin.

CONCLUSION

At the end of research study we concluded that by lowering blood pressure, body weight, low density lipoprotein cholesterol and raising high density lipoprotein cholesterol, further steps of development of atherosclerosis may be slow down or stopped eventually leading to morbidity or mortality due to myocardial infarction.

REFERENCES

1. B. J. Wu, L. Yan, F. Charlton, P. Witting, P. J. Barter, and K. A. Rye. Evidence That Niacin Inhibits Acute Vascular Inflammation and Improves Endothelial Dysfunction Independent of Changes in Plasma Lipids**.** Arterioscler Thromb Vasc Biol 2010; 30(5): 968 - 975.
2. P. Natarajan, K. K. Ray, and C. P. Cannon. High-Density Lipoprotein and Coronary Heart Disease: Current and Future Therapies**.** J. Am. Coll. Cardiol. 2010; 55(13): 1283 - 1299.
3. W. R. Hiatt, A. T. Hirsch, M. A. Creager, S. Rajagopalan, E. R. Mohler, C. M. Ballantyne, J. G. Regensteiner, D. Treat-Jacobson, and R. A. Dale. Effect of niacin ER/lovastatin on claudication symptoms in patients with peripheral artery disease Vascular Medicine 2010; 15(3): 171 - 179.
4. A L. Gould, J. Koglin, R. P Bain, C.-A. Pinto, Y. B Mitchel, R. C Pasternak, and A. Sapre. Effects of sources of variability on sample sizes required for RCTs, applied to trials of lipid-altering therapies on carotid artery intima-media thickness. Clinical Trials 2009; 6(4): 305 - 319.
5. L. Yvan-Charvet, J. Kling, T. Pagler, H. Li, B. Hubbard, T. Fisher, C. P. Sparrow, A. K. Taggart, and A. R. Tall. Cholesterol Efflux Potential and Antiinflammatory Properties of High-Density Lipoprotein After Treatment With Niacin or Anacetrapib**.** Arterioscler Thromb Vasc Biol 2010; 30(7): 1430 - 1438.
6. K.Prasad. Flax Lignan Complex Slows Down the Progression of Atherosclerosis in Hyperlipidemic Rabbits**.** Journal of Cardiovascular Pharmacology and Therapeutics 2009; 14(1): 38 - 48.
7. G.S.Goumas. Is There Evidence-based Hypolipidemic Treatment With Clinical Benefit Beyond Statins? Angiology 2009; 60(1): 93 - 98.
8. J. K. Duggal, M. Singh, N. Attri, P. P. Singh, N. Ahmed, S. Pahwa, J. Molnar, S. Singh, S. Khosla, and R. Arora. Effect of Niacin Therapy on Cardiovascular Outcomes in Patients With Coronary Artery Disease**.** Journal of Cardiovascular Pharmacology and Therapeutics 2010; 15(2): 158 - 166.
9. T. A. Jacobson. A "Hot" Topic in Dyslipidemia Management--"How to Beat a Flush": Optimizing Niacin Tolerability to Promote Long-term Treatment Adherence and Coronary Disease Prevention**.** Mayo Clin. Proc. 2010; 85(4): 365 - 379.
10. S. A. Sorrentino, C. Besler, L. Rohrer, M. Meyer, K. Heinrich, F. H. Bahlmann, M. Mueller, T. Horvath, C. Doerries, M. Heinemann, *et al.* Endothelial-Vasoprotective Effects of High-Density Lipoprotein Are Impaired in Patients With Type 2 Diabetes Mellitus but Are Improved After Extended-Release Niacin Therapy Circulation 2010; 121(1): 110 - 122.
11. S. Lamon-Fava, M. R. Diffenderfer, P. H. R. Barrett, A. Buchsbaum, M. Nyaku, K. V. Horvath, B. F. Asztalos, S. Otokozawa, M. Ai, N. R. Matthan, *et al.*. Extended-Release Niacin Alters the Metabolism of Plasma Apolipoprotein (Apo) A-I and ApoB-Containing Lipoproteins Arterioscler Thromb Vasc Biol 2008; 28(9): 1672 - 1678.
12. L.-H. Zhang, V. S. Kamanna, M. C. Zhang, and M. L. Kashyap. Niacin inhibits surface expression of ATP synthase {beta} chain in HepG2 cells: implications for raising HDL. J. Lipid Res. 2008; 49(6): 1195 - 1201.
13. J. G. Richman, M. Kanemitsu-Parks, I. Gaidarov, J. S. Cameron, P. Griffin, H. Zheng, N. C. Guerra, L. Cham, D. Maciejewski-Lenoir, D. P. Behan, *et al.*. Nicotinic Acid Receptor Agonists Differentially Activate Downstream Effectors. J. Biol. Chem 2007; 282(25): 18028 - 18036.
14. J. McKenney. New Perspectives on the Use of Niacin in the Treatment of Lipid Disorders**.** Arch Intern Med 2004; 164(7): 697 - 705.
15. M. E Mcgovern. Review: Use of nicotinic acid in patients with elevated fasting glucose, diabetes, or metabolic syndrome The British Journal of Diabetes & Vascular Disease 2004; 4(2): 78 - 85.
16. L. Saucan and E. A. Brinton. Lp A-I and Niacin: New Views of an Antiatherogenic Duo. Arterioscler Thromb Vasc Biol, November 1, 2001; 21(11): 1707 - 1709.
17. T. Sakai, V. S. Kamanna, and M. L. Kashyap. Niacin, but Not Gemfibrozil, Selectively Increases LP-AI, a Cardioprotective Subfraction of HDL, in Patients With Low HDL Cholesterol. Arterioscler Thromb Vasc Biol 2001; 21(11): 1783 - 1789.